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Queen Thomas
Printed Name

Queen Thomas
Signature

PATENT APPLICATION

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

The Accompanying Application

(continuation of Appl. No. 09/761,903)

Applicant: Mark Laurence Brader

For: INSOLUBLE INSULIN COMPOSITIONS

Docket No.: X-11232B

PRELIMINARY AMENDMENT

Assistant Commissioner for Patents
Washington, D. C. 20231

Sir:

Prior to calculating the claim fee for the continuation application filed herewith, please amend the accompanying application as follows.

Please debit our deposit account no. 05-0840 for all filing and claim fees.

In the Specification

At page 1, after the Title, insert the following new paragraph.

--This application is a continuation of U.S. Application No. 09/761,903, filed January 17, 2001 (allowed), which is a divisional of U.S. Application No. 09/177,685, filed October 22, 1998, which issued as U.S. Patent No. 6,268,335. This application claims priority benefit of U.S. Application No. 09/761,903, U.S. Application No. 09/177,685, U.S. Application No. 60/063,104, filed October 24, 1997, and U.S. Application No. 60/088,930, filed June 11, 1998, the content of each of which is hereby incorporated by reference.--

In the Claims

Cancel claims 1-84 without prejudice to or disclaimer of the subject matter therein, and add the following new claims 85 - 118.

--85. (New) A microcrystal comprising:

a) B29-Nε-tetradecanoyl-des(B30)-human insulin;

b) a complexing compound;

c) a hexamer-stabilizing compound; and

d) a divalent metal cation.

86. (New) The microcrystal of Claim 85, wherein the complexing compound is protamine which is present at about 0.15 mg to about 0.5 mg per 3.5 mg of B29-Nε-tetradecanoyl-des(B30)-human insulin.

87. (New) The microcrystal of Claim 86, wherein the divalent metal cation is zinc, which is present at about 0.3 mole to about 0.7 mole per mole of B29-Nε-tetradecanoyl-des(B30)-human insulin.

88. (New) The microcrystal of Claim 87, wherein the hexamer-stabilizing compound is a phenolic preservative selected from the group consisting of phenol, m-cresol, o-cresol, p-cresol, chlorocresol, methylparaben, and mixtures thereof and is present in sufficient proportions with respect to the B29-Nε-tetradecanoyl-des(B30)-human insulin to facilitate formation of the R6 hexamer conformation.

89. (New) The microcrystal of Claim 85, wherein the microcrystal has rod-like morphology.

90. (New) The microcrystal of Claim 85, wherein the microcrystal has irregular morphology.

91. (New) A suspension formulation comprising an insoluble phase and a solution phase, wherein the insoluble phase is comprised of the microcrystal of Claim 85, and the solution phase is comprised of water.

92. (New) A suspension formulation comprising an insoluble phase and a solution phase, wherein the insoluble phase is comprised of the microcrystal of Claim 86 and the solution phase is comprised of water.

93. (New) The suspension formulation of Claim 92, wherein the solution phase is further comprised of a phenolic preservative at a concentration of about 0.5 mg per mL to about 6 mg per mL of solution, a pharmaceutically acceptable buffer, and an isotonicity agent.

94. (New) The suspension formulation of Claim 93, wherein the solution phase is further comprised of insulin, an insulin analog, an acylated insulin, or an acylated insulin analog.

95. (New) The suspension formulation of Claim 94, wherein the solution phase is comprised of insulin.

96. (New) The suspension formulation of Claim 96, wherein the solution phase is comprised of an insulin analog.

97. (New) The suspension formulation of Claim 96, wherein the insulin analog is a monomeric insulin analog.

98. (New) The suspension formulation of Claim 97, wherein the insulin analog is LysB28,ProB29-human insulin analog.

99. (New) The suspension formulation of Claim 91, wherein the solution phase is further comprised of zinc and protamine, wherein the ratio of zinc to B29-Nε-tetradecanoyl-des(B30)-human insulin in the suspension formulation is from about 5 to about 7 mole of zinc atoms per mole of B29-Nε-tetradecanoyl-des(B30)-human insulin, and the ratio of protamine to B29-Nε-tetradecanoyl-des(B30)-human insulin in the suspension formulation is from about 0.25 mg to about 0.5 mg per mg of B29-Nε-tetradecanoyl-des(B30)-human insulin.

100. (New) A process for preparing the microcrystal of Claim 85 comprising:

a) dissolving B29-Nε-tetradecanoyl-des(B30)-human insulin, a hexamer-stabilizing compound, and a divalent metal

cation in an aqueous solvent having a pH that will permit the formation of hexamers of B29-Nε-tetradecanoyl-des(B30)-human insulin, and

b) adding a complexing compound.

101. (New) A process for preparing the microcrystal of Claim 85 comprising:

a) dissolving B29-Nε-tetradecanoyl-des(B30)-human insulin, a hexamer-stabilizing compound, and a divalent metal cation in an aqueous solvent having a pH that will not permit the formation of hexamers of B29-Nε-tetradecanoyl-des(B30)-human insulin, and

b) adjusting the pH to between about 6.8 and about 7.8; and

c) adding a complexing compound.

102. (New) A method of treating diabetes comprising administering the formulation of Claim 91 to a patient in need thereof in a quantity sufficient to regulate blood glucose levels in the patient.

103. (New) An amorphous precipitate comprising:

a) B29-Nε-tetradecanoyl-des(B30)-human insulin;

b) a complexing compound;

c) a hexamer-stabilizing compound; and

d) a divalent metal cation.

104. (New) The amorphous precipitate of Claim 103, wherein the complexing compound is protamine which is present at about 0.15 mg to about 0.5 mg per 3.5 mg of B29-Nε-tetradecanoyl-des(B30)-human insulin.

105. (New) The amorphous precipitate of Claim 104, wherein the divalent metal cation is zinc, which is present at about 0.3 mole to about 0.7 mole per mole of B29-Nε-tetradecanoyl-des(B30)-human insulin.

106. (New) The amorphous precipitate of Claim 105, wherein the hexamer-stabilizing compound is a phenolic preservative selected from the group consisting of phenol, m-cresol, o-cresol, p-cresol, chlorocresol, methylparaben, and mixtures thereof and is present in sufficient proportions with respect to the B29-Nε-tetradecanoyl-des(B30)-human insulin to facilitate formation of the R6 hexamer conformation.

107. (New) A suspension formulation comprising an insoluble phase and a solution phase, wherein the insoluble phase is comprised of the amorphous precipitate of Claim 103, and the solution phase is comprised of water.

108. (New) A suspension formulation comprising an insoluble phase and a solution phase, wherein the insoluble phase is comprised of the amorphous precipitate of Claim 104 and the solution phase is comprised of water.

109. (New) The suspension formulation of Claim 108, wherein the solution phase is further comprised of a phenolic preservative at a concentration of about 0.5 mg per mL to about 6 mg per mL of solution, a pharmaceutically acceptable buffer, and an isotonicity agent.

110. (New) The suspension formulation of Claim 109, wherein the solution phase is further comprised of insulin, an insulin analog, an acylated insulin, or an acylated insulin analog.

111. (New) The suspension formulation of Claim 111, wherein the solution phase is comprised of insulin.

112. (New) The suspension formulation of Claim 110, wherein the solution phase is comprised of an insulin analog.

113. (New) The suspension formulation of Claim 112, wherein the insulin analog is a monomeric insulin analog.

114. (New) The suspension formulation of Claim 113, wherein the insulin analog is LysB28,ProB29-human insulin analog.

115. (New) The suspension formulation of Claim 107, wherein the solution phase is further comprised of zinc and protamine, wherein the ratio of zinc to B29-Nε-tetradecanoyl-des(B30)-human insulin in the suspension formulation is from about 5 to about 7 mole of zinc atoms per mole of B29-Nε-tetradecanoyl-des(B30)-human insulin, and the ratio of protamine to B29-Nε-tetradecanoyl-des(B30)-human insulin in the suspension formulation is from about 0.25 mg to about 0.5 mg per mg of B29-Nε-tetradecanoyl-des(B30)-human insulin.

116. (New) A process for preparing the amorphous precipitate of Claim 104 comprising:

a) dissolving B29-Nε-tetradecanoyl-des(B30)-human insulin, a hexamer-stabilizing compound, and a divalent metal cation in an aqueous solvent having a pH that will permit the formation of hexamers of B29-Nε-tetradecanoyl-des(B30)-human insulin, and

b) adding a complexing compound.

117. (New) A process for preparing the amorphous precipitate of Claim 104 comprising:

a) dissolving B29-Nε-tetradecanoyl-des(B30)-human insulin, a hexamer-stabilizing compound, and a divalent metal cation in an aqueous solvent having a pH that will not permit the formation of hexamers of B29-Nε-tetradecanoyl-des(B30)-human insulin, and

b) adjusting the pH to between about 6.8 and about 7.8; and

c) adding a complexing compound.

118. (New) A method of treating diabetes comprising administering the formulation of Claim 107 to a patient in need thereof in a quantity sufficient to regulate blood glucose levels in the patient.--

Remarks

I. Status Of The Claims

Claims 1-84 have been canceled, and new claims 85-118 have been added. Claims 85-118 are pending in the present application.

II. Support For The Amendment

Support for new claims 85-118 is found in the specification, for example, at page 9, lines 3-6, 22 and 23; page 24, line 32; page 25, lines 2, 9 and 19; and page 26, lines 18-22, 32 and 33.

In addition, support for new claims 85-118 is found in claims 17, 20-22, 24-26, 54 and 64-69.

No new matter has been added by this amendment.

Respectfully submitted,

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12/6/01

Claims As Filed

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thereof and is present in sufficient proportions with respect to the B29-Nε-tetradecanoyl-des(B30)-human insulin to facilitate formation of the R6 hexamer conformation.

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93. (New) The suspension formulation of Claim 92, wherein the solution phase is further comprised of a phenolic preservative at a concentration of about 0.5 mg

per mL to about 6 mg per mL of solution, a pharmaceutically acceptable buffer, and an isotonicity agent.

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99. (New) The suspension formulation of Claim 91, wherein the solution phase is further comprised of zinc and

protamine, wherein the ratio of zinc to B29-Nε-tetradecanoyl-des(B30)-human insulin in the suspension formulation is from about 5 to about 7 mole of zinc atoms per mole of B29-Nε-tetradecanoyl-des(B30)-human insulin, and the ratio of protamine to B29-Nε-tetradecanoyl-des(B30)-human insulin in the suspension formulation is from about 0.25 mg to about 0.5 mg per mg of B29-Nε-tetradecanoyl-des(B30)-human insulin.

100. (New) A process for preparing the microcrystal of Claim 85 comprising:

a) dissolving B29-Nε-tetradecanoyl-des(B30)-human insulin, a hexamer-stabilizing compound, and a divalent metal cation in an aqueous solvent having a pH that will permit the formation of hexamers of B29-Nε-tetradecanoyl-des(B30)-human insulin, and

b) adding a complexing compound.

101. (New) A process for preparing the microcrystal of Claim 85 comprising:

a) dissolving B29-Nε-tetradecanoyl-des(B30)-human insulin, a hexamer-stabilizing compound, and a divalent metal cation in an aqueous solvent having a pH that will

not permit the formation of hexamers of B29-Nε-tetradecanoyl-des(B30)-human insulin, and

b) adjusting the pH to between about 6.8 and about 7.8; and

c) adding a complexing compound.

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a) B29-Nε-tetradecanoyl-des(B30)-human insulin;

b) a complexing compound;

c) a hexamer-stabilizing compound; and

d) a divalent metal cation.

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105. (New) The amorphous precipitate of Claim 104, wherein the divalent metal cation is zinc, which is present at about 0.3 mole to about 0.7 mole per mole of B29-Nε-tetradecanoyl-des(B30)-human insulin.

106. (New) The amorphous precipitate of Claim 105, wherein the hexamer-stabilizing compound is a phenolic preservative selected from the group consisting of phenol, m-cresol, o-cresol, p-cresol, chlorocresol, methylparaben, and mixtures thereof and is present in sufficient proportions with respect to the B29-Nε-tetradecanoyl-des(B30)-human insulin to facilitate formation of the R6 hexamer conformation.

107. (New) A suspension formulation comprising an insoluble phase and a solution phase, wherein the insoluble phase is comprised of the amorphous precipitate of Claim 103, and the solution phase is comprised of water.

108. (New) A suspension formulation comprising an insoluble phase and a solution phase, wherein the insoluble phase is comprised of the amorphous precipitate of Claim 104 and the solution phase is comprised of water.

109. (New) The suspension formulation of Claim 108, wherein the solution phase is further comprised of a phenolic preservative at a concentration of about 0.5 mg per mL to about 6 mg per mL of solution, a pharmaceutically acceptable buffer, and an isotonicity agent.

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115. (New) The suspension formulation of Claim 107, wherein the solution phase is further comprised of zinc and protamine, wherein the ratio of zinc to B29-Nε-tetradecanoyl-des(B30)-human insulin in the suspension formulation is from about 5 to about 7 mole of zinc atoms per mole of B29-Nε-tetradecanoyl-des(B30)-human insulin, and the ratio of protamine to B29-Nε-tetradecanoyl-des(B30)-human insulin in the suspension formulation is from about 0.25 mg to about 0.5 mg per mg of B29-Nε-tetradecanoyl-des(B30)-human insulin.

116. (New) A process for preparing the amorphous precipitate of Claim 104 comprising:

a) dissolving B29-Nε-tetradecanoyl-des(B30)-human insulin, a hexamer-stabilizing compound, and a divalent metal cation in an aqueous solvent having a pH that will permit the formation of hexamers of B29-Nε-tetradecanoyl-des(B30)-human insulin, and

b) adding a complexing compound.

117. (New) A process for preparing the amorphous precipitate of Claim 104 comprising:

a) dissolving B29-Nε-tetradecanoyl-des(B30)-human insulin, a hexamer-stabilizing compound, and a divalent metal cation in an aqueous solvent having a pH that will not permit the formation of hexamers of B29-Nε-tetradecanoyl-des(B30)-human insulin, and

b) adjusting the pH to between about 6.8 and about 7.8; and

c) adding a complexing compound.

118. (New) A method of treating diabetes comprising administering the formulation of Claim 107 to a patient in need thereof in a quantity sufficient to regulate blood glucose levels in the patient.